Acquired Hemophilia A Developed Post COVID-19 Vaccine: An Extremely Rare Complication

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Abstract

Acquired hemophilia A (AHA) is a rare autoimmune bleeding disorder caused by circulating autoantibodies (inhibitor) directed against coagulation factor VIII (FVIII). We report a 39-year-old single female who presented to emergency department with sudden onset gross hematuria 10 days following her first dose of Pfizer-BioNTech severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mRNA (coronavirus disease 2019 (COVID-19)) vaccine. Coagulation profile revealed isolated prolongation of the activated partial thromboplastin time due to FVIII deficiency with normal von Willebrand factor and activity. Mixing study revealed time-dependent inhibitor pattern that was successively identified as directed against FVIII using the Nijmegen-modified Bethesda assay. FVIII inhibitor in a titer of 17.2 Bethesda Units/mL was detected. While thrombosis is a frequent complication of severe COVID-19 infection, on the other hand, bleeding is rare in the setting of COVID-19 infection/vaccination with no anticoagulants. Till date, a couple of cases of acquired hemophilia developed after receiving mRNA derived COVID-19 vaccines (Pfizer-BioNTech SARS-CoV-2 mRNA vaccine and Moderna mRNA vaccines) had been reported. It is important to raise the awareness about this rare side effect that might be directly induced by the mRNA COVID-19 vaccine or that the vaccine could have triggered it in a genetically predisposed individual. We recommend considering screening for an inhibitor (by mixing study) in cases with otherwise unexplained onset hemorrhagic disorder and/or isolated activated partial thromboplastin time prolongation.

Keywords: Acquired hemophilia A; Hemorrhage; Immune dysregulation; COVID-19 vaccine

Introduction

Acquired hemophilia A (AHA) is a rare bleeding disorder caused by circulating autoantibodies (inhibitor) directed against coagulation factor VIII (FVIII) [1, 2]. AHA is frequently associated with pregnancy, systemic autoimmune disease, malignancies, infections and drug. Two peaks in AHA incidence are usually seen, one in pregnancy/post-partum and the other with elderly [1].

Unlike hemarthrosis which is a common feature of congenital hemophilia, mucocutaneous bleeding is the hallmark of AHA which is characterized by hemorrhage into skin, soft tissues, and mucous membranes leading to ecchymosis, hematomas, epistaxis, melena, and gross hematuria [1].

The mechanism of the production of FVIII inhibitor in a particular individual is not obvious but may be linked to certain genetic polymorphisms (e.g., human leucocyte antigen (HLA), cytotoxic T lymphocyte-associated antigen 4 (CTLA-4)) and/or autoreactive CD4^{+} (helper) T lymphocytes [3]. Vaccines have long been implicated in generating autoantibodies. Pfizer-BioNTech mRNA vaccine induces the production of spike-specific IgG antibody within 7 - 21 days after first dose [4]. This is the second case of AHA developing after receiving the Pfizer-BioNTech severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mRNA vaccine. In addition, another case of AHA developed post mRNA-1273 SARS-CoV-2 vaccine manufactured by Moderna had been recently reported [5].

Case Report

Investigations

The case was a 39-year-old single female with no known medical illness, no personal or family history of bleeding diathesis, no history of anticoagulants, and no history of malignancy. The patient had recently received her first dose of Pfizer-BioNTech SARS-CoV-2 mRNA (coronavirus disease 2019 (COVID-19)) at end of May 2021; 10 days after she presented to emergency department with lower quadrant pain and 3 days history of frank hematuria.

The patient was admitted and prescribed antibiotics (cefuroxime). Her symptoms improved except for hematuria which became more gross and she described passing clots with urine.

The patient reported no previous history of bruising or bleeding from any other site, but she lately had heavier regular menstrual periods (5 - 6 days), probably related to multiple fibroids. Her physical examination was unremarkable. She has no previous history of pregnancy or giving birth. Previous routine coagulation tests were normal.

Laboratory workup revealed normal liver and kidney functions. Complete blood count showed moderate microcytic hypochromic anemia (hemoglobin 8.6 g/dL, normal range: 12 - 15), normal white blood cell count and normal platelets count at 342×10^9/L (normal range 150 - 500 $\times 10^9$/L). Autoimmune screen was negative: rheumatoid factor < 10 IU/mL (0 - 14), anti-cyclic citrullinated peptides (anti-CCP) antibody < 8 U/mL (0 - 17); anti-connective tissue disease (anti-CTd) was negative, complement C3 (1.54 g/L), C4 (H 0.41 g/L) with negative anti-neutrophilic cytoplasmic autoantibody (ANCA). Ferritin level was high at 1,182.0 µg/L with mildly elevated lactate dehydrogenase (LDH) at 229 U/L (135 - 214). Glucose-6-phosphate dehydrogenase (G6PD) screen was negative. Flow cytometry analysis revealed no immunophenotypic evidence of paroxysmal nocturnal hemoglobinuria.

Diagnosis

Coagulation profile revealed a normal international normalized ratio (INR), normal prothrombin time (PT) at 11.0 s (9.7 - 11.8) and persistently prolonged activated partial thromboplastin time (aPTT) on repeated testing ranging between 65 and 72.2 s (normal: 24.6 - 31.2). Lupus anticoagulant was not detected.

Fibrinogen was high at 5.73 g/L (1.7 - 4.2) with normal platelet function assay (PFA) at 134.8% (82-150%), normal von Willebrand antigen at 129.7% (53.7-148.5%) and activity (function) of 120% (43.6-140.5%). FIX was 108.8%, FV was 198.6%, and FVII was 134.8% with persistently low factor VIII at 2% (70-150%).

Mixing study performed in two-time frames immediately (at zero hour) resulted in corrected aPTT followed by no correction of aPTT after 2-h incubation, a pattern consistent with the presence of time-dependent inhibitor.

The presence of inhibitor pattern in mixing study together with low FVIII level had indicated measuring the intensity of the inhibitor level using the Nijmegen-modified Bethesda assay.

The autoantibody against FVIII (FVIII inhibitor) in a titer of 17.2 Bethesda Units/mL (BU/mL) was detected. Bethesda assay was repeated using the chromogenic assay and the titer was 18 BU/mL. Overall findings were consistent with AHA.

Treatment

Since the bleeding severity ranges from mild to moderate, it was decided to monitor the patient for now with a consideration of autoantibodies eradication therapy with corticosteroids (prednisone 1 mg/kg) and rituximab 375 mg/m² if bleeding gets worse.

Follow-up and outcomes

The patient did not take the second dose of COVID-19 vaccine. A spontaneous recovery was achieved after almost 2 months after the initial presentation with normalization of aPTT (30.2 s) and FVIII level (78.8%).

Discussion

AHA is a rare autoimmune disorder, mediated by autoantibodies against key functional epitopes of coagulation FVIII. Radwi et al [6] had recently reported the first case of AHA in a 69-year-old gentleman who presented with a bruising on wrist and muscular hematomas 9 days after receiving Pfizer mRNA COVID-19 vaccine. Another case of AHA developed in an elderly male patient with a background of autoimmune diseases (polymyalgia rheumatica) and hepatitis C virus, 8 days after receiving the first dose of the mRNA-1273 SARS-CoV-2 (Moderna) vaccine [5]. It is worth noting that AHA in a young female (as the case reported here) with no pregnancy and in the absence of comorbidities is even more rare.

The growing literature clearly emphasizes the immune dysregulation role of COVID-19 that may lead to immune hyperactivation and cytokine storm described in severe/fatal infection. In the same context, our literature search revealed two cases of AHA associated with COVID-19 virus infection, one case with *de novo* AHA [7] and in the other case, the COVID-19 infection had provoked re-appearance of FVIII inhibitor and recurring AHA [8]. The COVID-19 virus-induced immune dysregulation is reinforced by the documented recent association between immune thrombocytopenic purpura (ITP) and COVID-19 [9]. Other forms of autoimmune disorders in association with COVID-19 infection, including development of lupus anticoagulants [10], autoimmune hemolytic anemia [11] and Guillain-Barre syndrome [12] are increasingly reported in the literature.

With the worldwide progressive increase in COVID-19 vaccination, the expanding literature about autoimmune disorders developed post COVID-19 vaccination becomes more evident. Numerous cases of ITP have been reported to the vaccine Adverse Event Reporting System after receiving the Pfizer-BioNTech and Moderna COVID-19 vaccines [13].

The two large recently published case series have established high levels of autoantibodies against antigenic complexes of platelet factor 4 (PF4) in all patients in these two series [14, 15].

The pathogenesis of genetically engineered mRNA vaccine-induced autoantibody is not fully understood but it is probably caused by molecular mimicry as well as activation of quiescent auto-reactive T and B cells, i.e., antibodies against SARS-CoV-2 spike glycoproteins cross-reacting with host peptide protein sequences that are structurally similar of coagulation factors or red blood cell/platelet membranes, giving rise to autoimmune mechanism of the reported cases of acquired hemophilia, immune hemolytic anemia, and ITP, respectively [16, 17].

It is possible that in the case reported here the mRNA COVID-19 vaccination had provoked *de novo* immune-mediated adverse event or had triggered a pre-existing underlying

dysregulated immune pathway. In a similar scenario, Franchini et al [8] had reported re-appearance of AHA triggered by acute SARS-CovV-2 infection.

Learning points

With the current widespread COVID-19 vaccination campaigns worldwide, it is important to raise the awareness about this rare side effect that may be directly induced by the mRNA COVID-19 vaccines or that the vaccine could have triggered it in a genetically predisposed individual.

Similar to other vaccines and existing literature, a causative link between vaccination and autoimmune disorders cannot be established. Although it is very difficult to certainly conclude the causal relationship between the genetically engineered mRNA COVID-19 vaccines and AHA, and that the development of FVIII inhibitors post vaccination could be only a coincidental event, we believe that the association is valid in the reported case. This is supported by absence of the common causes of AHA in our patient who did not have history of previous pregnancies with negative autoimmune screen and no malignancies. Additionally, the symptoms started 10 days after receiving the vaccine which is the estimated reported time for antibody development post COVID-19 vaccine and was also similar to that reported in the first case of AHA post Pfizer-BioNTech SARS-CoV-2 mRNA vaccine (9 days) and the second AHA case developed post Moderan COVID-19 vaccine (8 days). While thrombosis is a frequent complication of severe COVID-19 infection, on the other hand, bleeding is rare in the setting of COVID-19 infection/vaccination with no anticoagulants. We recommend considering screening for an inhibitor (by mixing study) in cases with otherwise unexplained onset hemorrhagic disorder and/or isolated aPTT prolongation. It is crucial to highlight the possible rare association between mRNA COVID-19 vaccine and AHA. However, until reported in a larger number of patients, it is wise to consider the likelihood that this association is coincidental.

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Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Informed Consent

A waived consent form was approved according to our institution medical research requirements.

Author Contributions

DS diagnosed the case, formulated the paper, did the literature review and wrote the manuscript; AA performed clinical examination, data review and follow-up. DA performed the technical examination of coagulation laboratory testing. FI reviewed the manuscript.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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